

# AN UNUSUAL CAUSE OF HYPOKALEMIA IN AN ELDERLY MAN WITH HYPERTENSION

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## SUMMARY

Hypokalemia in the elderly usually results from gastrointestinal loss or the use of diuretics. However, primary aldosteronism should be considered in hypertensive patients with metabolic alkalosis and unexplained hypokalemia with hyperkaliuresis. We report a 63 year-old hypertensive man with such metabolic findings. The transtubular potassium concentration gradient and serum aldosterone level were higher than normal. Abdominal computed tomography showed bilaterally enlarged adrenal glands, and a nuclear medicine study supported the diagnosis of bilateral adrenal hyperplasia. [International Journal of Gerontology 2007; 1(4): 168–172]

**Key Words:** hypertension, hypokalemia, metabolic alkalosis, primary aldosteronism

## Introduction

Hypokalemia in the elderly is usually due to gastrointestinal loss or the administration of diuretics. Hypertension in the elderly is usually assumed to be essential primary hypertension, and the cause is not defined<sup>1</sup>. However, the association of hypertension, unexplained hypokalemia, and metabolic alkalosis should raise the possibility of secondary hypertension caused by overproduction of aldosterone.

We present an elderly patient with hypertension who was admitted with a brainstem infarction and found to have hypokalemia, prompting a search for the cause.

## Case Report

A 63-year-old Chinese man complained of right-sided clumsiness, slurred speech, and general weakness on the

day of admission. He had no recent history of vomiting or diarrhea. He had had hypertension for 5 years that was treated with an unknown medication. He admitted that his blood pressure was poorly controlled. He had no other known illnesses but had been a heavy smoker for more than 15 years. He denied use of any other medications. On admission, his blood pressure was 184/64 mmHg, and he was alert, although his speech was slurred. Examination of the chest, heart and abdomen were unremarkable. Neurologic examination disclosed right hemiplegia. The electrocardiogram revealed normal sinus rhythm. He was found to be markedly hypokalemic (serum potassium, 1.9 mEq/L), but the serum sodium (145 mEq/L), blood urea nitrogen (10 mg/dL) and creatinine (0.9 mg/dL) were within normal limits. Magnetic resonance imaging and angiography of the brain disclosed a recent ischemic infarct involving the ventral pons secondary to occlusion of the midbasilar artery. Echocardiography revealed no evidence of intracardiac thrombus. Amlodipine 5 mg was given daily to control the blood pressure, and potassium chloride was given by slow intravenous infusion, which raised the serum potassium level to 3.0 mEq/L. This was then switched to oral potassium 30 mEq daily, but the serum potassium remained at

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2.5 to 2.6 mEq/L. Further investigation was undertaken to investigate the hypokalemia.

The spot urine potassium indicated hyperkaliuresis, and the patient had metabolic alkalosis with normal peripheral plasma renin activity (PRA) and an elevated plasma aldosterone concentration (PAC) (Table). Abdominal computed tomography was then performed to identify the source of the hyperaldosteronism. The hypodense adrenal glands were enlarged bilaterally to about 2 cm, and the radiologist suggested that there might be bilateral adrenal adenomas (Figure 1). Magnetic resonance imaging and magnetic resonance angiography of the renal arteries also demonstrated bilateral adrenal enlargement with normal renal arteries (Figure 2). Serial nuclear medicine scans were performed for 4 days following intravenous injection of  $^{131}\text{I}$ -labeled 6-beta-iodomethyl-19-norcholesterol (NP-59), while the

patient was given dexamethasone. This revealed faint visualization of the adrenal glands on the third day and clearer visualization on the fourth day, consistent with bilateral adrenal hyperplasia (Figure 3).

Spironolactone 150 mg daily was begun and then tapered to 50 mg daily. The hypokalemic metabolic alkalosis subsequently resolved without the need for further potassium replacement. The patient's blood pressure was also easily controlled with the combination of spironolactone and amlodipine 5 mg daily.

## Discussion

This elderly patient's hypertension, hypokalemia, and metabolic alkalosis were due to overproduction of aldosterone, in this case by hyperplasia of the adrenal

Table. Laboratory evaluation of persistent hypokalemia in a patient with hypertension

	Patient's value	Reference value
Urine output (mL/day)	2,100	
TTKG	8.9	<3
Serum osmolality (mOsm/kg)	295	285–295
Urine osmolality (mOsm/kg)	351	300–900
Spot urine potassium (mEq/L)	27.6	<15
Supine PAC (pg/mL)	322	29–162
Supine PRA (pg/mL)	3.49	1.1–20
Cortisol at 8 a.m. ( $\mu\text{g/dL}$ )	17.5	5–25
24 hr urine VMA (mg/day)	6.0	1.0–7.5
pH	7.492	7.38–7.44
$\text{PaCO}_2$ (mmHg)	39.1	35–45
Bicarbonate (mmol/L)	29.2	21–28

TTKG=transtubular potassium concentration gradient; PAC=plasma aldosterone concentration; PRA=peripheral plasma renin activity; VMA=vanillylmandelic acid;  $\text{PaCO}_2$ =arterial carbon dioxide partial pressure.



Figure 1. Computed tomography of the abdomen demonstrating bilaterally enlarged, hypodense adrenal glands measuring about 2 cm (white arrows).

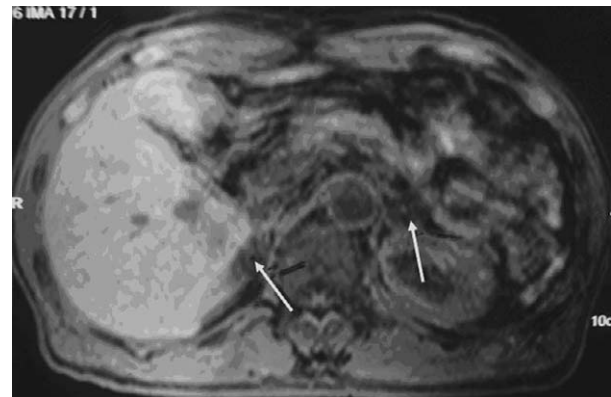


Figure 2. Low signal intensity seen in bilaterally enlarged adrenal masses on T1- and T2-weighted images with signal loss on out-of-phase images (white arrow).

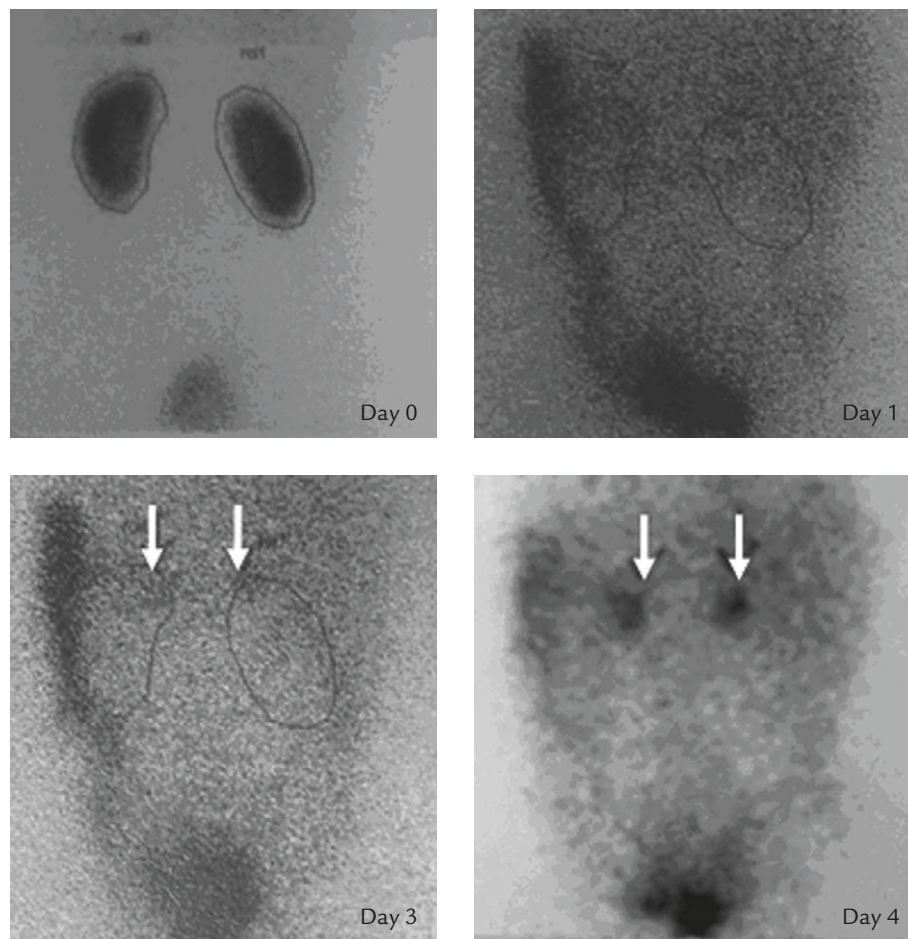


Figure 3. Serial scintigraphic scans from day 1 to day 4 after intravenous injection of  $^{131}\text{I}$ -6-beta-iodomethyl-19-norcholesterol (NP-59) with dexamethasone suppression revealing faint visualization of the adrenal glands bilaterally on day 3 and greater visibility on day 4 (white arrows), compatible with bilateral adrenal hyperplasia.

glands. The case illustrates the diagnostic approach in patients with this constellation of findings. It is also a good reminder that while such disorders are common, we should be alert for the occasional patient who presents with an unexpected disorder. It is rare to find a secondary cause of hypertension in the elderly, but our patient's findings gave important clues that led to the correct diagnosis.

A careful medication history is always important, particularly in the elderly who are taking many different drugs, a number of which can contribute to hypokalemia. Certain medications, such as  $\beta_2$  agonists, theophylline, chloroquine and laxatives, cause potassium to shift into cells with resulting low serum levels. Other medications, such as aldosterone analogues, hydrocortisone, aminoglycosides, cisplatin, carbenoxolone, glycyrrhizic acid (the active agent of licorice) and a number of diuretics, cause hypokalemia secondary to increased potassium excretion. As is unfortunately

often the case, our patient did not know what medication he was taking for his hypertension, so we did not know if he had been on a diuretic.

The key turning point in his course was discovering that his hypokalemia was resistant to potassium replacement. The next step was then to determine if he was excreting excess potassium in his urine. Hyperkaliuresis is defined as a urine potassium excretion of more than 25 to 30 mEq/day<sup>2</sup>, a transtubular potassium gradient (TTKG) of more than 3.0, or a spot urine potassium to creatinine ratio of more than 2.0. These tests are helpful, although the limitations must be kept in mind. Incomplete urine collection, intracellular potassium shift or interference by drugs may affect the results of a 24-hour urine collection. Variations in muscle mass, severe rhabdomyolysis, volume depletion, variable urine volumes, and renal impairment may influence the result of the spot urine potassium-to-creatinine ratio. While a TTKG of greater than 3 indicates hyperkaliuresis

in patients with normal to high urine osmolality, it is less reliable in those with low urine osmolality<sup>3</sup>. Our patient's 24-hour potassium excretion was nearly 58 mEq and his TTKG was 8.9 in the presence of normal serum osmolality, so the diagnosis of hyperkaliuresis in his case was clear.

According to a new diagnostic algorithm for evaluating hypokalemia<sup>2</sup>, once hyperkaliuresis has been demonstrated in a patient with hypertension and metabolic alkalosis, the PAC and PRA levels are measured and an aldosterone-to-renin ratio (ARR) calculated. An ARR of greater than 30 is suggestive of primary aldosteronism, but values between 20 and 35 constitute a "gray zone"<sup>4</sup>. There are several caveats to keep in mind when interpreting the ratio, including the patient's posture when the blood is drawn, the timing of the test, medications, extremely low PRA, and age<sup>4</sup>. In patients with extremely low PRA (less than 0.1 ng/mL/hour), some authors suggested that an ARR of more than 20 in combination with a PAC greater than 15 ng/dL constitute a positive result in positive screening for primary aldosteronism<sup>4</sup>. False positives have been attributed to treatment with  $\beta$ -blockers, methyldopa or clonidine, chronic renal failure, potassium loading, and Gordon's syndrome, while a falsely negative ARR may be seen during treatment with diuretics (including spironolactone) and calcium channel blockers (especially dihydropyridines), severe dietary salt restriction, renovascular hypertension, pregnancy, and malignant hypertension<sup>5</sup>. There is some disagreement, however, on whether anti-hypertensive medications, including  $\beta$ -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, aldosterone antagonist and diuretics, must be discontinued before the test is performed<sup>6</sup>.

Since the ARR is only a screening test, some authors recommend that confirmatory tests be required to diagnose or exclude primary aldosteronism<sup>4</sup>. These include a fludrocortisone or dexamethasone suppression test and an oral or intravenous saline loading test. The fludrocortisone suppression test is reportedly more reliable than a saline loading test<sup>7</sup> and is positive if aldosterone levels are higher than 5 ng/dL and PRA levels less than 1.0 ng/mL/hour after administration of fludrocortisone. The complexity and costs associated with the confirmatory tests have led some experts to suggest a trial of an aldosterone antagonist first, with other studies undertaken only if this treatment fails. However, this treatment is not without side effects, including hyperkalemia, gynecomastia and prerenal

azotemia, so others would recommend confirmation of the diagnosis and identification of the source<sup>5</sup>.

By definition, primary hyperaldosteronism is the overproduction of aldosterone due to adrenal aldosterone-producing tumor or hyperplasia in the absence of an elevated PRA. This is in contrast to secondary aldosteronism caused by elevated renin levels, as seen in malignant hypertension, renal artery stenosis, renin-secreting tumor, and pheochromocytoma. The prevalence of primary aldosteronism in an unselected hypertensive population is around 5% to 40%<sup>8</sup>. Although hypokalemia is a hallmark of primary aldosteronism, a reported 7% to 38% of patients with primary aldosteronism have normokalemia<sup>9</sup>. This makes hyperaldosteronism particularly difficult to detect in the elderly, as the normal potassium level would not prompt a search for a secondary cause of hypertension. Causes of primary aldosteronism include adrenal carcinoma (quite rare but suspected when an adrenal tumor is larger than 4 cm), familial hyperaldosteronism types I and II, adrenal hyperplasia, and aldosterone-producing adenoma<sup>10</sup>. Adenoma has conventionally thought to be the most common cause of primary aldosteronism, but bilateral adrenal hyperplasia is increasingly being recognized as a fairly frequent entity<sup>11</sup>, although this may simply reflect a more precise case finding rather than a true increased incidence. Adenomas are commonly seen in middle-aged people who have hypokalemia, minimal aldosterone suppressibility by volume loading, increased body sodium content, and an inverse relationship between aldosterone and angiotensin. Bilateral adrenal hyperplasia is seen more commonly in the elderly, in whom hypokalemia may not be as prevalent. The aldosterone is often partially suppressible with volume loading, the total sodium content is normal, and there is a direct relation between aldosterone and angiotensin<sup>8</sup>. The definitive test to distinguish between an aldosterone-producing adenoma and bilateral adrenal hyperplasia is adrenal venous sampling<sup>8</sup>, which can detect adrenal adenomas of less than 1 cm or tumors that may be too small to be identified on conventional imaging. The distinction between an adenoma and bilateral hyperplasia is a vital one, as the former is treated surgically, while the latter is not. However, in some cases, it may be wise to proceed directly to a trial of an aldosterone antagonist, reserving venous sampling for those who fail to respond to medical treatment<sup>5</sup>.

Our patient had a very high ARR and did respond very well to spironolactone. We did give dexamethasone

to suppress his adrenal glands, but only as part of the nuclear medicine study, which helped to confirm the diagnosis of bilateral adrenal hyperplasia. Adrenal venous sampling was not necessary in his case.

In our patient, the presence of hypertension and hypokalemia that was unresponsive to potassium replacement was the key to diagnosing his primary aldosteronism. His metabolic abnormalities prompted testing which demonstrated hyperkaliuresis, and the subsequent investigations were straightforward. The challenge, of course, is deciding whether to screen elderly patients with hypertension who are not hypokalemic, as recommended by some authors<sup>11</sup>.

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